Amendments to the Sequence Listing:

Please enter the attached Sequence Listing, numbered as pages 1-52.

Please substitute the attached Sequence Listing section for the Sequence Listing filed April 19, 2000.

A new computer-readable form is also attached.

REMARKS

Claims 13-16, 20-22, 30, 43-50, 53-60, and 62-71, 73-75 and 77-79 presently appear in this application. Claims 62, 64, 70 and 71 have been allowed. Claims 46, 53, 56-58, 65-68 and 73-75 have been objected to, and the remaining claims have been rejected. Reconsideration and allowance of all the claims now present in the case are hereby respectfully urged.

Briefly, the present invention relates to cDNA sequences that encode polypeptides that bind to TRAF2 and inhibit or increase activity of NF-κB as well as the polypeptides encoded by those DNA sequences. Preferably, the polypeptide is NIK. The invention also relates to antibodies, methods of identification and screening, and anti-sense DNA.

Claims 13-16, 20-22, 30, 43-45, 47-50, 54, 55, 59, 60, 63, 69 and 77-79 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for the reasons of record in the official action of September 5, 2002, and June 27, 2003. The examiner states that the claims still recite a polypeptide that binds to TRAF2 and either inhibits or increases the activity of NF-κB, comprising an amino acid sequence of a fragment of one of three specified sequences.

The examiner states that there is no length assigned to the fragment and, therefore, the term may encompass fragments as small as two amino acids. This part of the rejection is respectfully traversed.

The only part of claim 69 that is subject to the instant written description rejection is section c), relating to fragments of a). The examiner has not objected to paragraph b), which is directed to analogs having no more than ten changes in the amino acid sequence of a), each said change being a substitution, deletion or insertion of an amino acid, which analog binds to TRAF2 and either inhibits or increases the activity of NF-κB. It is apparent that the examiner concedes that the structure of the analogs satisfies the written description requirement, presumably for the reasons set forth in Example 14 of the Examiner Training Materials relating to the written description requirement.

However, by the same logic as is set forth in Example 14 of the Examiner Training Materials, the fragments should also be acceptable. Just as procedures for making variants that have 95% identity to a sequence and retain its activity are conventional in the art, so are procedures for making fragments of a given sequence that retain their activity. The genus of fragments is not expected to be

inordinately large since all of the fragments must possess the specified activity and have a sequence that is a part of the sequence of the polypeptides specifically set forth in paragraph a) of claim 69. The specification teaches how to determine whether any given fragment binds to TRAF2 and either inhibits or increases the activity of NF-κB. Thus, by the same logic as is provided in Example 14 of the Examiner Training Materials, one of skill in the art would conclude that applicants were in possession of the necessary common attributes possessed by the members of genus.

The structure of the fragments is known because their sequence must appear as part of one of the three sequences set forth in paragraph a). All three of these sequences have over 400 amino acid residues. For a protein of 400 amino acids, 95% identity allows twenty amino acids to vary among twenty different amino acids. The genus of all fragments is much smaller than this. This is another reason why, if the functional analogs of Example 14 of the Examiner Training Materials are acceptable, the functional fragments must be all the more acceptable. Fragments only involve deletions from the N- or C-terminal. They do not involve substitutions or insertions. It is a routine matter to produce fragments by deleting a single amino acid residue from either end of the full sequence and testing it to see

if it retains its activity. Assays for testing binding to TRAF2 and its effect on the activity of NF-κB are set forth in the specification. Accordingly, applicants have supplied an adequate written description for the entire genus of paragraph c) of claim 69.

As to the examiner's comment that there is no length assigned to the fragment, this is not correct as the length of the fragment is functionally set forth. Claim 69 requires that the fragment bind to TRAF2 and either inhibit or increase the activity of NF-κB. No fragment as small as two amino acids can possibly have this activity. Those of ordinary skill in the art are well aware that an entire polypeptide can be trimmed one amino acid at a time from the N-terminal or the C-terminal end, for example, by appropriate enzymes, and then tested for TRAF2 binding and effect on NF-κB activity. Once the fragment is too small to have such activity, it is not necessary to test smaller fragments.

It should be noted that this examiner's position about the reference to active fragments failing to comply with the written description requirement, is substantially different from the position of her colleagues who have allowed claims with such language in other cases from the laboratory of the present inventors, which cases have very

similar specifications with respect to support for active fragments. In this regard, the examiner's attention is invited to U.S. patents 6,399,327; 6,479,632; 6,586,571; 6,734,174; and 6,762,283. Perhaps a conference with some of these other examiners will be helpful in formulating a consistent policy with respect to such fragments.

For all of these reasons, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner states that claim 20 recites a NIK polypeptide wherein the polypeptide has at least part of the amino acid sequence of SEQ ID NO:7 and, therefore, the examiner considers that this may encompass a single amino acid of SEQ ID NO:7.

Claim 20 is dependent from claim 53, which is dependent from claim 69. Thus, the reference in claim 20 to "at least part of the amino acid sequence" would cover the entire SEQ ID NO:7 (i.e., the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:6) or a fragment thereof. However, claim 69 makes it clear that any fragment must bind to TRAF2 and either inhibit or increase the activity of NF-κB. As claim 20 is a dependent claim, it cannot broaden the definition of fragment and, therefore, the examiner's interpretation of claim 20 is incorrect.

Nevertheless, in order to eliminate any possible indefiniteness with respect to claim 20, it has now been amended to specify that the polypeptide is the polypeptide encoded by the nucleotide sequence of SEQ ID NO:6 (which is the same as the amino acid sequence of SEQ ID NO:7 but uses language that appears in claim 69) or a fragment thereof that binds to TRAF2 and either inhibits or increases the activity of NF-κB. It is thus clear from its face that the subject of this claim is no broader than claim 69 from which claim 53 depends. Accordingly, claim 20 is supported by an adequate written description at least for all of the reasons discussed above with respect to claim 69. Reconsideration and withdrawal of this part of the rejection are therefore respectfully urged.

The examiner states that claims 22 and 50 recite antibodies and "active fragments" of said antibodies that are specific for the polypeptides of the invention, but, apart from further trial and error experimentation, applicants have not demonstrated that they were in possession of the full scope of "active fragments" that are encompassed by the claims. This part of the rejection is respectfully traversed.

The antibody art is extremely well defined for those of ordinary skill in the art, and applicants have made

no new inventions in the field of antibodies, other than specifying a new antigen from which to raise the antibodies. The present specification, at page 73 (of the substitute specification), paragraph [0133], states that fragments of antibodies may be provided by any known techniques, such as but not limited to enzymatic cleavage, peptide synthesis or recombinant techniques. Furthermore, at page 76, paragraphs [0140] and [0141] of the specification speak of fragments such as the Fab and $F(ab')_2$ that are capable of binding antigen.

Those of ordinary skill in the art are well aware that the term "active fragments", when referred to in relation to antibodies, means that the fragment must be capable of binding the antigen. Because of the well-developed nature of antibody technology, anyone of ordinary skill in the art in possession of an antibody is readily in possession of all of its active fragments without undue experimentation. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

The examiner states that claim 30 recites "a sequence encoding TRAF2", but the structure of a TRAF2 DNA sequence that is required to practice the claimed method is not recited in the claims. Therefore, the examiner states that the TRAF2 encoding sequence encompasses all allelic,

polymorphic and splice variants of TRAF2 encoding sequences, including all species variants of the TRAF2 encoding sequence, and the specification as filed does not describe the structures of the full scope of sequences encompassed by this claim. This part of the rejection is respectfully traversed.

The present specification is not directed to TRAF2. TRAF2 is prior art to the present invention. See page 2, paragraph [0003] of the present specification. Claim 30 is directed to a method of screening for polypeptides that will bind directly to TRAF2. It is not necessary for a specification to set forth the sequence of a compound that is in the prior art and whose sequence is part of the prior art. Note particularly WO 95/33051, referenced in paragraph [0003] of the present specification. Note also paragraph [0176] at page 92 of the substitute specification that specifies exactly where the human TRAF2 sequence is known in the prior art. If an allelic variation exists or a single nucleotide polymorphism that is non-synonymous exists that encodes a protein that the art recognizes as TRAF2 and has all the properties of TRAF2, there is no reason why this sequence cannot be used in the process of claim 30. Claim 30 is directed to a screening process and not to a particular sequence. The invention is the idea of using

this screening process on the known protein TRAF2 and is not directed to a sequence of TRAF2. Claim 30 has now been amended to refer specifically to human TRAF2, as is supported in paragraph [0176].

Furthermore, when one gives the name of a protein, one usually is referring to the sequence that has the most common residue at every position, which is usually that sequence specified for the protein in databases, such as SWISS-PROT, which is mirrored in GENBANK.

As to whether the inventors were in possession of the full genus of nucleotide sequences that encode the amino acid sequence of human TRAF2, the examiner's attention is invited to MPEP §2163.II.A.3.a.ii. (8th Ed, Rev. 2 2004), where it states:

> [I]f an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species.

See also *In re Wallach*, 378 F.3d 1330, 1334 (Fed. Cir. 2004) which cites this section with approval.

Accordingly, as the sequence of TRAF2 is known, it is clear that the present inventors were in possession of all of the nucleotide sequences that encode it. For all of these reasons, reconsideration and withdrawal of this part of the rejection are also respectfully urged.

The examiner states that claim 45 recites a method that comprises the use of a polypeptide comprising at least a portion of TRAF2 having the amino acid residues 222-501 of TRAF2, and claim 48 recites a method for identifying and producing a molecule capable of directly or indirectly either inhibiting or increasing the cellular activity that is changed or mediated by NIK by screening for a molecule capable of either inhibiting or increasing activities that are changed or mediated by NIK. The examiner states, however, that there is no specific amino acid sequence set forth in these claims that correspond to TRAF2 or NIK and, therefore, these claims encompass TRAF2 and NIK proteins including all allelic and polymorphic variants, including proteins isolated from all species expressing this protein. The examiner also states that, with respect to "the portion" in claims 45 and 47, the claims read on portions of any length whereby the polypeptide used in the claimed method may comprise any length of the portions. This part of the rejection is respectfully traversed.

With respect to claim 45, as has been discussed above, the sequence of TRAF2 forms no part of the present invention. Paragraphs [0003] and [0176] have been cited above with respect to the known identity of this sequence. Furthermore, primers for isolating the human TRAF2 sequence by PCR are set forth in paragraph [0176]. Claim 45 has also been amended to refer only to human TRAF2. Accordingly, for the same reasons as discussed above with respect to claim 30, it is not necessary to set forth a sequence for human TRAF2 in claim 45. Human TRAF2 and its sequence are part of the prior art and applicants are in possession of this sequence just as is everyone else of ordinary skill in the art, as evidenced by the specific reference to publications setting forth this sequence in the present specification.

With respect to claim 48, this claim has now been amended to specify that NIK is SEQ ID NO:7. Accordingly, this part of the rejection has now been obviated.

With respect to "portion", claim 45 has been amended to refer to "the portion", i.e., the portion which has the sequence of amino acids 222-501 of TRAF2, not a portion of that portion. Accordingly, this part of the rejection has now been obviated.

With respect to claim 47, reference to a portion of the NIK sequence has been deleted, thus obviating this part of the rejection.

Reconsideration and withdrawal of these parts of the rejection are therefore respectfully urged.

The examiner states that claim 54 is directed to a DNA sequence encoding a polypeptide in accordance with claim 69. The examiner essentially refers to the previous reasons for rejecting claim 69 for lack of written description and states that, since the genus of polypeptides encompassed by claim 69 are not adequately described, the DNA sequences encoding as set forth in claim 54 are also not adequately described. Furthermore, the examiner states that due to the degeneracy of the genetic code, there are an exponential number of polynucleotides that may function to encode a single amino acid sequence and that there could be multiple introns in the pre-mRNA encoding a polypeptide, the sequence of which cannot be predicted by the structure of the amino acid sequence, and, based on these considerations, the amino acid sequences encompassed by claim 69 cannot be used to predict the structures of the full scope of DNA sequences that encode these polypeptides. This part of the rejection is respectfully traversed.

Applicants have already discussed above why the present specification provides adequate written description for the presently claimed fragments of paragraph c) of claim 69. Accordingly, for the same reason that the written description rejection of claim 69 must be withdrawn as discussed above, so must this rejection of claim 54 be withdrawn insofar as it is based on the lack of written description for the polypeptides of claim 69.

With respect to the examiner's comments about the degeneracy of the genetic code, the examiner's attention is invited to the portion of MPEP §2163 quoted above, as well as the case of *In re Wallach, supra*. Once one is in possession of each of the polypeptides recited in claim 69, one is automatically in possession of the entire genus of DNA that encode them. The examiner's comments about introns in pre-mRNA encoding a polypeptide is not understood as these introns do not encode the polypeptide. Claim 54 is only directed to DNA sequences encoding a polypeptide. Accordingly, reconsideration and withdrawal of this part of the rejection are also respectfully urged.

The examiner states that claims 77-79 recite DNA sequences encoding a polypeptide in accordance with clam 73, 74 or 75 and that claim 63 recites a DNA sequence encoding the polypeptide of claim 62. The examiner states that these

DNA claims are objectionable for the reasons as presented with respect to claim 54. This part of the rejection is respectfully traversed.

For the same reasons as discussed above with respect to claim 54, this rejection of claims 63 and 73-79 must also be withdrawn. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

The examiner states that paragraph (2) of claim 59 reads on a DNA sequence that encodes a polypeptide that is purely defined by function and that applicants have not provided a direct correlation between the recited function, namely wherein said polypeptide binds TRAF2, and either inhibits or increases the activity of NF-κB and is encoded by a DNA sequence capable of binding to a DNA sequence capable of binding to the nucleotide sequence of SEQ ID NO:6. Therefore, the examiner states that the full scope of DNA sequences can only be identified by trial and error experimentation. This part of the rejection is respectfully traversed.

The second paragraph of claim 59 requires that the polypeptide have a sequence capable of binding to a DNA sequence encoding the sequence of a polypeptide in accordance with claim 53 under moderately stringent conditions. Not only must it have this structure, but it

must also bind to TRAF2 and either inhibit or increase the activity of NF-κB. Claim 59 has now been amended in order to clarify this, although the scope of the claim has not been changed. The examiner has withdrawn the indefiniteness rejection of "moderately stringent conditions". The present specification at paragraph [0068], bridging pages 36 and 37, states that hybridizable DNA sequences include DNA sequences that have a relatively high homology to the native TRAF2-binding proteins cDNA sequence. Thus, the polypeptide of claim 59(2) is not described solely by function, but is described by a sequence that is capable of binding to a DNA sequence encoding the sequence of (1) under moderately stringent conditions, which polypeptides will necessarily have a great degree of homology with the polypeptide of (1). Once such polypeptides are found, they are simply tested for binding to TRAF2 and either inhibition or increasing of the activity of NF-κB. Accordingly, claim 59 also fulfills the written description requirement of 35 U.S.C. §112. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

Claims 20 and 52 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that claim 20 is indefinite in reciting "at least a part of the amino acid sequence of SEQ ID NO:7".

The examiner considers this indefinite as Figure 6 shows that SEQ ID NO:7 is the predicted amino acid sequence encoded by SEQ ID NO:6, and it is unclear what other polypeptides might be encompassed by claim 20.

In attempt to clarify claim 20, it has now been amended to specify that the polypeptide is the polypeptide encoded by the nucleotide sequence of SEQ ID NO:6 (so as to use language that better tracks claim 53) or a fragment thereof that binds to TRAF2 and either inhibits or increases the activity of NF-κB. Claim 53 includes polypeptides encoded by the nucleotide sequence of SEQ ID NO:6 as the polypeptide of paragraph a) and includes analogs, fragments and derivatives thereof. Claim 20 reads only on the full sequence of the polypeptide or a fragment thereof as defined in paragraph c) of claim 69, which definition has been physically incorporated into claim 20, again to eliminate any possible indefiniteness. Accordingly, it is believed that the scope of claim 20 is now clear and this rejection has now been obviated.

The examiner states that claim 52 has insufficient antecedent basis for the limitation "the sequence encoded by SEQ ID NO:3".

Claim 52 has now been deleted, thus obviating this rejection.

The examiner has objected to claim 70 as it makes reference to Tables IA and IB and claims, where possible, should be complete in themselves.

Claim 70 has now been amended to physically insert the contents of Tables IA and IB, thus obviating this rejection. Reconsideration and withdrawal thereof are respectfully urged.

The examiner states that the application contains sequence disclosures that fail to comply with the requirements of 37 C.F.R. §1.821-1.825. The examiner states that sequences at page 36, line 31, and page 37, line 31, of four amino acids are disclosed in the specification but do not appear in the sequence listing.

The present specification has now been amended to clarify that the sequence at page 36, line 31, of the originally filed application (page 66, line 20, of the substitute specification) has been given SEQ ID NO:21, and the sequence at page 37, line 31, of the originally filed application, which appears at line 18 of page 68 of the substitute specification, is SEQ ID NO:22.

Applicants have added into the present specification a new paper copy Sequence Listing section according to 37 C.F.R. §1.821(c) as new pages 1-52. This new paper copy includes sequences 21 and 22. Furthermore,

attached hereto is a 3 1/2" disk containing the "Sequence Listing" in computer readable form in accordance with 37 C.F.R. §1.821(e). The paper and computer readable form are attached hereto as Appendix A.

The following statement is provided to meet the requirements of 37 C.F.R. §1.821(f) and 1.821(g) §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is the same as the attached substitute paper copy of the sequence listing.

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and

the results of his or her sequence search against a database containing known natural sequences.

It is noted that the examiner has indicated that claim 62, 64, 70 and 71 are free of the prior art and allowable once claim 70 has been amended to overcome the objection due to a minor informality. The examiner states that claims 46, 53, 56-58, 65-68 and 73-75 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form, including all of the limitations of the base claim and any intervening claims. As it is believed that the base claim and the intervening claims have now been shown to be allowable hereinabove, these claims have not yet been rewritten into independent form.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are hereby earnestly solicited.

Respectfully submitted,

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